REMARKS

Information Disclosure Statement

The Examiner stated that the Information Disclosure Statement filed on 9/25/03 failed to comply with the provisions of 37 C.F.R. §1.97-1.98 because the International Search Report is not a publicly published document. The Examiner stated that she reviewed the International Search Report, but did not officially consider it on the merits.

The Applicants thank the Examiner for officially considering the three references reported in the International Search Report, which the Applicants separately listed on the Information Disclosure Statement. The Applicants, however, respectfully submit that the International Search Report is also appropriate for official consideration, as it was in fact publicly published as part of publication number WO 03/004990 A3, on January 16, 2003. International Search Reports are routinely considered by the Patent Office as appropriate submissions for an Information Disclosure Statement. *See, e.g.*, U.S. Patent Nos. 6,461,630; 6,503,735; 6,504,079; 6,352,972; 5,916,553; 6,779,179; 6,779,055.

Claim Objections

Claims 4, 14, and 19 are objected to based on minor typographical errors. [Official Action, p. 3]. The Applicants have amended claims 4, 14, and 19 to correct these errors. In claim 4, "dimineralizing" was changed to "demineralizing". In claim 14, a comma was added after "TGF-ß". In claim 19, "pictogram" was changed to "picogram".

Clarifying Amendments

Applicants have amended claims 3, 11, 17, and 31 in order to further clarify the invention and expedite examination. Claim 3 has been amended to recite "...autograft, allograft, or xenograft bone, said bone being cortical bone, cancellous bone, or a combination thereof." This amendment finds support in the specification at page 11, lines 27-29 ("In one principal embodiment of the invention, the implant is an implant composed substantially of mineralized or demineralized cortical bone, cancellous bone, or cortical-cancellous bone, whether in the form of an autograft, allograft or xenograft, as these terms

are understood in the art."). Claim 11 was amended to recite "a combination thereof", rather than "combinations." In claim 17, "ELIZA" was amended to "ELISA" to correct for a typographical error. This term was correctly indicated in the specification at page 14, lines 21-22 ("Likewise, enzyme-linked immunoadsorbent assays (ELISAs) known in the art, immunoprecipitation assays, and the like may interchangeably be applied according to this invention at this stage, provided that it is determined that interfering materials do not destroy the accuracy and precision of the quantitative detection method chosen."). In claim 31, Applicants deleted redundant and/or unnecessary claim language.

Summary of Bases for Rejection

Claims 1-23 and 31 are rejected under 35 U.S.C. §112, second paragraph, as being allegedly indefinite.

Claims 1, 12-23, and 31 are rejected under 35 U.S.C. §112, first paragraph, on the grounds that the specification allegedly fails to provide an enabling disclosure for the claimed subject matter.

Claims 1-6, 19-20, 22-23, and 31 are rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Zhang et al., *A Quantitative Assesment of Osteoinductivity of Human Demineralized Bone Matrix*, Journal of Periodontology, Vol. 68(11), pp. 1076-1084 (Nov. 1997). The Applicant will address each of the above bases of rejection in sections I - III, respectively.

I. 35 U.S.C. §112, second paragraph

(a) *Claim 1 (line 9) and Claim 23 (line 7)*

Claims 1 (line 9) and claim 23(line 7) recited the phrase "use of complex biological living materials," which the Examiner alleges is vague and indefinite. The Applicants have amended claims 1 and 23 to recite instead that the quantifying step "occurs *in vitro* and does not require implantation of said materials *in vivo* or use of cell-based assays". This amendment finds support in the specification at ¶10 (page 11, lines 1-4) ("These cell-based and animal-based assays involve large amounts of work, take weeks to months to produce results, and are inherently irreproducible because they involve living or complex biological systems."). Applicants believe that this amendment sufficiently

defines the metes and bounds of the claim and overcomes the Examiner's rejection. The amendment makes clear that the invention avoids the inefficiency, reproducibility problems, and moral issues regarding the use of living test animals or cell cultures.

(b) *Claim 1 (line 12) and Claim 23 (line 10)*

Claim 1 (line 9) and claim 23 (line 10) recited the terms "corresponding" and "similar values" which the Examiner alleges are vague and indefinite. The Applicants have amended claims 1 and 23 to recite instead "converting the quantified concentration of at least one osteogenic factor to a value of osteogenic potential for said representative sampling based on a predetermined curve." This amendment finds support in original claim 1. The amendment clearly defines the scope of the claim by illustrating that an osteogenic potential value is computed by converting the osteogenic factor value obtained in step (b) based on a predetermined curve. Accordingly, Applicants submit that the amendment overcomes the Examiner's rejection on this basis.

(c) *Claim 4 (line 2)*

The Examiner alleges that the phrase "substantially demineralized" in Claim 4 (line 2) is vague and indefinite. The Applicants have amended claim 4 to recite "...demineralizing bone implant material to produce a demineralized bone implant matrix comprising a calcium concentration less than about 3 percent." This amendment finds support in the specification at paragraph 56, Example 1 (page 17, lines 21-22) ("Human cortical bone was ground into a powder using a proprietary mill and then demineralized by agitation in cold (4°C.) 0.5 N HCl until the calcium content was less than 3%."). Because the amendment clearly sets forth a range of calcium concentration, the Applicants believe that the Examiner's rejection is overcome.

(d) *Claim 10 (line 1) and Claim 11 (line 2)*

The Examiner alleges that the term "low" in claim 10 (line 1) and claim 11 (line 2) is vague and indefinite. The Applicants have amended these claims to recite "removing interfering non-osteogenic factor molecules...". This amendment finds support in the specification at ¶52 (page 14, lines 27-30) ("Where it is determined that interfering materials remain upon release of the osteogenic factors from the implant, these factors are removed by any of a number of standard methods known in the art which do not remove

the osteogenic factors from the implant releasate."). Applicants submit that the claim as amended is clear and definite, and that the Examiner's rejection is overcome.

(e) *Claim 13 (lines 1-2) and Claim 19 (lines 1-2)*

The Examiner rejected claims 13 and 19 based on alleged lack of antecedent basis for the terms "said at least one osteoinductive factor" and "said osteoinductive factors", respectively. Applicants have amended claims 13 and 19 to correctly recite "osteogenic" factor(s), for which claim 1 provides antecedent basis.

(f) *Claim 18 (line 3)*

Claim 18 (line 3) recites the phrase "under conditions", which the Examiner alleges is vague and indefinite. Applicants have amended claim 18 to recite in part "...contacting said at least one osteogenic factor with an antibody specific thereto such that specific binding of said antibody to said at least one osteogenic factor occurs, and quantitating the amount of said antibody specifically binding..." Applicants submit that the amended claim clearly and definitely defines the antibody binding step. This amendment finds support in original claim 18, and in the specification at page 16, line 5 ("and bound antibody is quantitated to provide a quantitative measure of the amount of osteogenic factor bound....")

II. 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 1, 12-23, and 31, alleging that the specification fails to provide an enabling disclosure for the full scope of the claims. [Official Action, pp. 6-7]. The Examiner acknowledges that the specification is enabled for bone implants, but alleges that it does not reasonably provide enablement for implant materials other than bone. [*Id.*]

In the interest of clear and expeditious examination, the Applicants have amended claims 1 and 23 to recite "[a]n *in vitro* method for quantifying the osteoinductive potential of a collection of like implant material comprising bone..." and have cancelled claim 2. Because, as the Examiner has acknowledged in the Official Action [Official Action, p. 6], the specification provides enabling disclosure for performing the claimed method on an implant material comprising bone, Applicants respectfully request the withdrawal of this basis of rejection.

III. 35 U.S.C. §102(b)

Claims 1-6, 19-20, 22-23, and 31 stand rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Zhang *et al.*, *A Quantitative Assesment of Osteoinductivity of Human Demineralized Bone Matrix*, Journal of Periodontology, Vol. 68(11), pp. 1076-1084 (Nov. 1997). The Examiner alleges that Zhang et al. discloses all of the elements of claims 1-6, 19-20, 22-23, and 31. Namely, the Examiner alleges that Zhang et al. discloses an *in vitro* method for quantifying the osteoinductive potential of demineralized bone matrix by quantifying the concentration of alkaline phosphatase via a protein assay.

However, "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP, §2131.01, citing *Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.3d 628, 631 (Fed. Cir. 1987). In the present case, each and every element of Applicants' claims are not found in Zhang *et al.*

Claims 1 and 23 (and all other dependent claims therein), require "quantifying the concentration of at least one osteogenic factor present in said implant releasate...". Osteogenic factors are described in the specification as "mammalian bone matrix-derived proteins which exhibit the ability to promote or stimulate local osteogenesis at sites of implantation in mammals." [Specification at page 6, lines 6-8, ¶12]. The present invention **directly** measures the actual growth factors responsible for bone induction to quantify the osteoinductive capacity of an implant prior to deployment *in vivo*.

In contrast, Zhang *et al.* does not directly measure an osteogenic factor. Zhang *et al.* **indirectly** measures osteogenic activity by measuring the enzyme alkaline phosphatase, which is produced by osteoblasts (bone forming cells) during bone growth. Alkaline phosphatase is not an osteogenic factor, since it does not directly promote or stimulate osteogenesis. Rather, it is the **indirect** product of osteogenesis. The Applicants' specification specifically distinguishes the prior arts' use of the **indirect** agent – alkaline phosphatase, stating:

> **Existing in vitro cell-based assays** have utilized methods that indirectly link osteogenic, osteoconductive, or osteoinductive implant activity with bone formation in vivo. Examples include measurement of **alkaline phosphatase** activity in cell cultures or proliferation of cancer cells. However, these assays have been

> found to show only **weak correlation** with in vivo bone induction in subsequent animal studies.
>
> [Specification at page 4, lines 28-31 to page 5, line 1, ¶10; emphasis added in bold].

Furthermore, Zhang *et al.* merely loosely correlated calcium production (not histological analysis and actual bone growth) to alkaline phosphatase concentrations. *See* Zhang *et al.*, p. 1082 ("In the current study, calcium contents of explants were used as the major indicator of osteoinductivity."). Zhang *et al.* do not disclose directly measuring bone growth factors nor converting the concentration of those factors directly to osteoinductivity. Significantly, the Zhang *et al.* reference only discloses a 74% correlation between alkaline phosphatase levels and *in vivo* measurement of calcium production. *See* Zhang *et al.*, p. 1083. The present invention, however, exhibits a correlation of greater than 94% for the range of probabilities of 50-60%, 95% for the range of 60-70%, and 100% at probability ranges higher than 70%. [Specification at page 18, lines 9-11, ¶56].

Furthermore, each of the claims of the present application, as amended, require avoiding the use of "cell-based assays." [Claims 1, 23]. The present application is distinguishable from the prior art in that the present *in vitro* assay method does not require the use of living test animals or cell cultures. Rather, the present invention preferably demineralizes the bone matrix to produce a releasate, and then directly quantifies growth factors using assays including, but not limited to ELISA assays (enzyme linked immunoadsorbant assay), radio-immunoassays, or immunoprecipitation assays. Zhang *et al.*, however, used a growing periosteal cell culture, from which alkaline phosphatase levels was measured.

For the foregoing reasons, the Zhang *et al.* reference is not anticipatory of any of the claims of the present application. Withdrawal of the rejection of claims 1-6, 19-20, 22-23, and 31 under 35 U.S.C. §102(b) is therefore appropriate, and allowance of claims 1-23 and 31 is respectfully requested.

CONCLUSION

Claims 1-23 and 31 stand rejected. Claims 1, 4, 10-14, 18-19, and 23 have been amended. Claim 37 has been added by amendment herein. Claim 2 has been canceled. Accordingly, claims 1-23, 31 and 37 are pending.

In view of the amendments and arguments provided herein, all bases for rejecting claims 1-23 and 31 under 35 U.S.C. §112, second paragraph, have been rebutted. In view of the amendments and arguments provided herein, all bases for rejecting claims 1, 12-23, and 31 under 35 U.S.C. §112, first paragraph, have been rebutted. In view of the amendments and arguments provided herein, all bases for rejecting claims 1-6, 19-20, 22-23, and 31 under 35 U.S.C. §102(b) have been rebutted. For the reasons stated herein, these bases for rejection should not be applied to new claim 37. The allowance of claims 1-23, 31 and 37 is respectfully requested.

Respectfully submitted,

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